

Collaborating with Academia

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Executive Director Molecular Genetics | Ultragenyx Pharmaceutical

November 7, 2023

Ultragenyx Pharmaceutical
RARE Entrepreneurship Bootcamp

Disclaimer



Opinions based on my
experiences and
perspective

A cynical tactic to
illustrate the nuances —
albeit factual — of
collaborating with
academic researchers

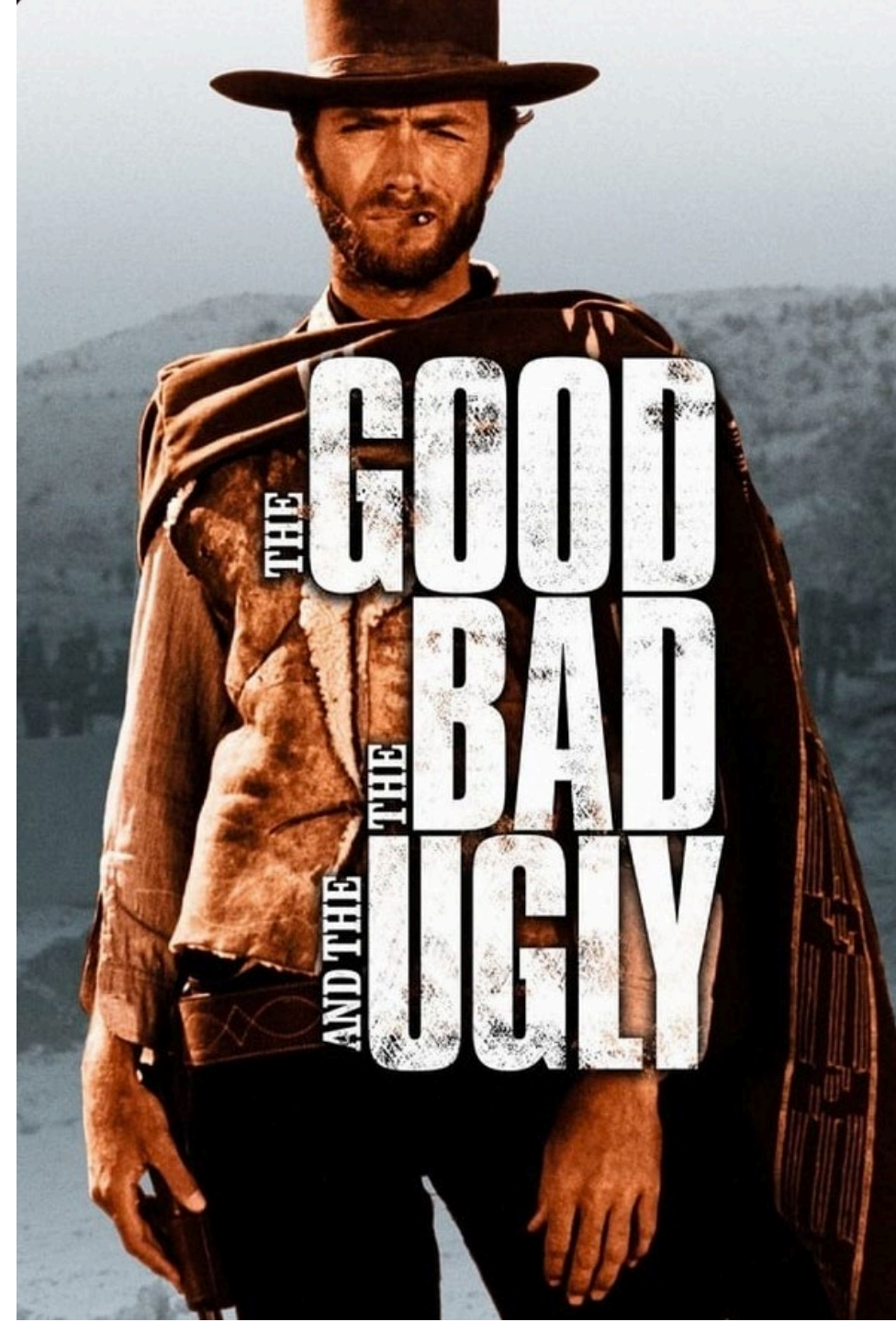
My Background

- Faculty Member, Texas A&M University (2008-present)
- Chief Scientific Officer, GeneTx Biotherapeutics (2017-2020)
- Executive Director Molecular Genetics, Ultragenyx Pharmaceutical (2020-present)

My Background

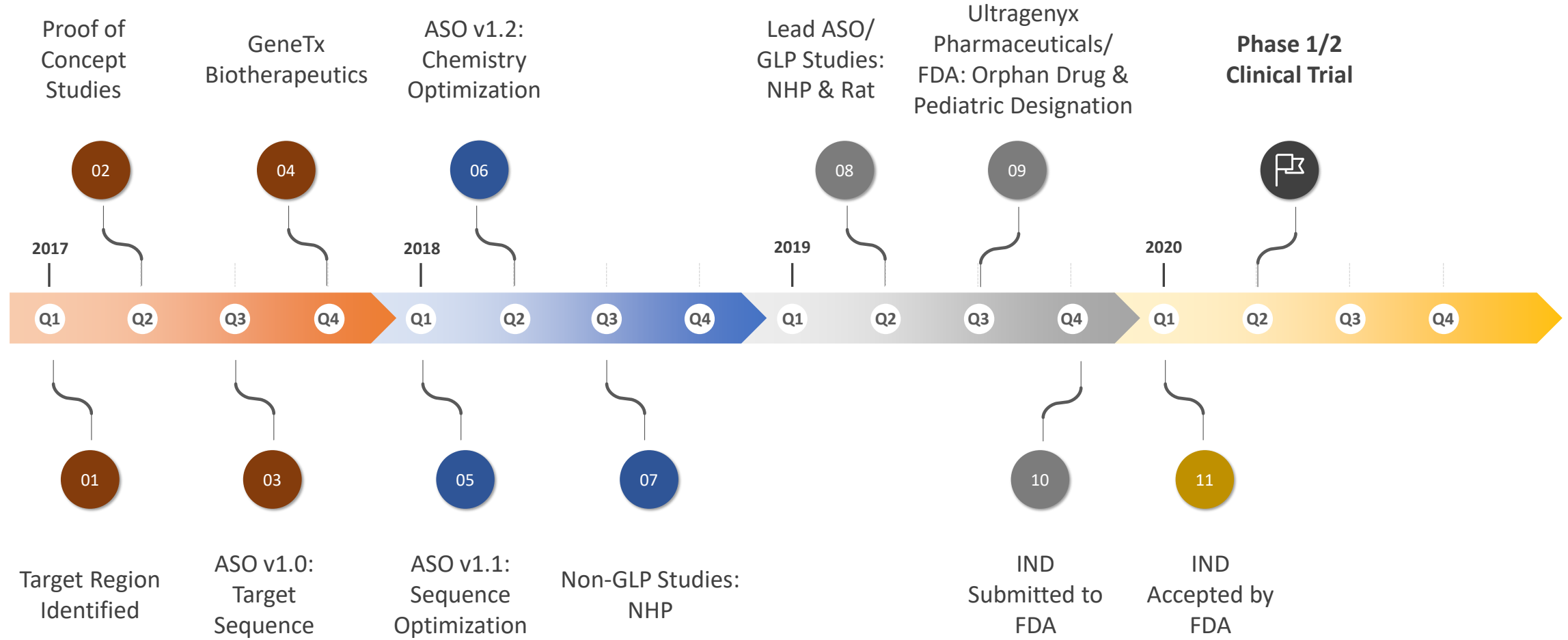
- Continuous funding from federal agencies, foundations, companies, and licensing agreements.
- 15 years collaborating with rare disease foundations.
- Lab invented the first investigational molecular therapy for Angelman syndrome to advance into clinical development.

Collaborating
with
Academia



The GOOD

The First Molecular Therapy for Angelman Syndrome to Advance into Clinical Development



the BAD and the UGLY

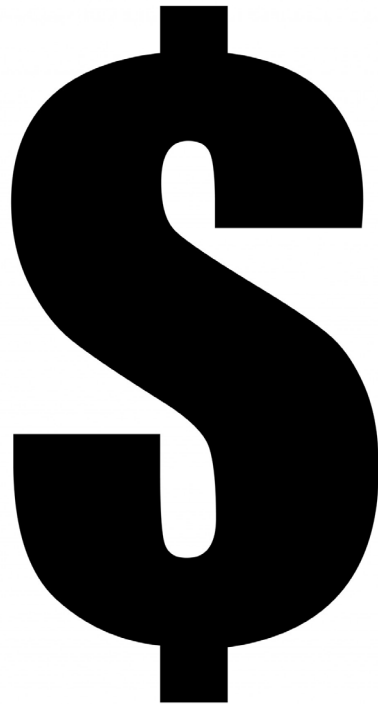
Academic Research

The largest flea markets in the world



Academic Research

The currency of our trade is measured in grant dollars and publications



Human Molecular Genetics, 2008, Vol. 17, No. 1 111–118
doi:10.1093/hmg/ddm288
Advance Access published on October 16, 2007

The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology

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Received August 24, 2007; Revised and Accepted September 27, 2007

Loss of function of the maternally inherited allele for the *UBE3A* ubiquitin ligase gene causes Angelman syndrome (AS), which is characterized by severe neurological impairment and motor dysfunction. In addition, *UBE3A* lies within chromosome 15q11–q13 region, where maternal, but not paternal, duplications cause autism. The *UBE3A* gene product, E6-AP, has been shown to function both as an E3 ligase in the ubiquitin proteasome pathway and as a transcriptional coactivator. However, the specific role of E6-AP in the brain, or how loss of function of E6-AP results in AS, is unclear. Herein, we show, using a recombinant transgenic mouse expressing a *Ube3a*^{YFP} fusion gene, that the maternal *Ube3a*^{YFP} allele is upregulated and preferentially expressed in neurons, and that the fusion protein, E6-AP:YFP, is enriched in the nucleus and dendrites *in vivo*. We also show that E6-AP:YFP localizes to the nucleus and to presynaptic and postsynaptic compartments in cultured hippocampal neurons. Furthermore, we show that cerebellar Purkinje cell number and dendritic branching are not affected in *Ube3a* maternal-deficient mice, but that dendritic spine development, including spine morphology, number and length, is affected on cerebellar Purkinje cells and on pyramidal neurons in the hippocampus and cortex. Collectively, these data suggest that the neurological deficits observed in AS patients and in AS mice may result from specific abnormalities in synaptic development and/or plasticity.

INTRODUCTION

Angelman syndrome (AS) is characterized by severe mental retardation, absence of speech, ataxia and a happy disposition (1,2). The AS gene, *UBE3A*, encodes the E6-AP ubiquitin ligase and is subject to genomic imprinting, with preferential maternal-specific expression in brain and, more specifically, in neurons but not in glia (3,4). Maternal but not paternal interstitial duplications of chromosome 15q11–q13 cause autism (5). These duplications encompass multiple genes, but *UBE3A* is a strong candidate to contribute to the autism phenotype in 15q11–q13 duplication cases based on its imprinted status and known causative role in AS (6). Autism spectrum disorders are seen with Prader–Willi syndrome and AS, the two phenotypes associated with paternal and maternal deletions of 15q11–q13, respectively (7,8).

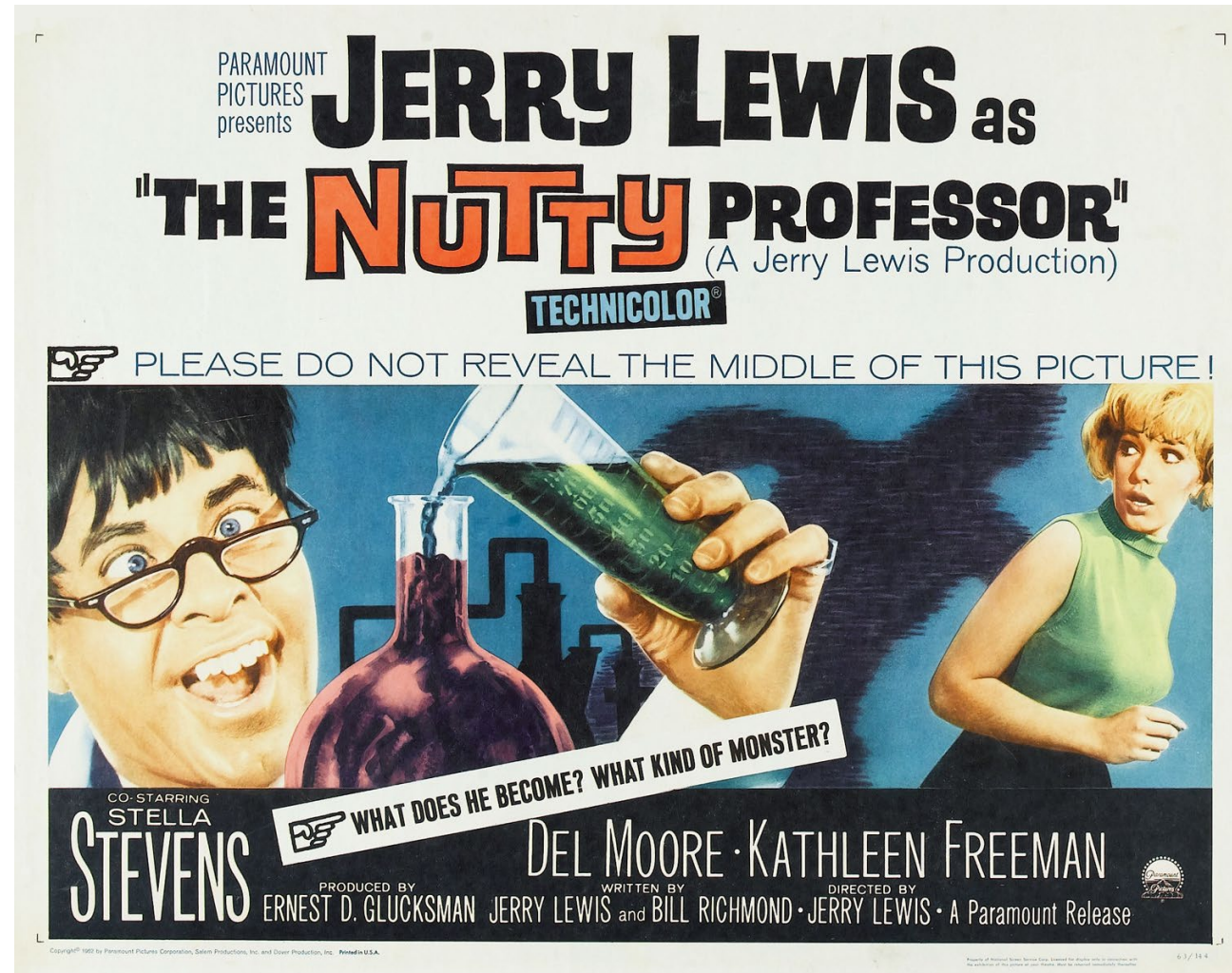
Mice with a maternal null mutation in *Ube3a* (AS mice) have defects in long-term potentiation (LTP) and manifest motor and behavioral abnormalities that parallel findings in AS in spite of normal cellular architecture in the brain (9). The neurological deficits in AS mice have been directly linked to the postsynaptic calcium/calmodulin kinase type 2 (CaMKII) signaling pathway, as AS mice have increased inhibitory phosphorylation of α CaMKII in the brain (10). Moreover, the learning and behavioral deficits present in AS mice can be rescued through a mutation in CaMKII that prevents its inhibitory phosphorylation (11). Other reports have linked E6-AP to various neurologically relevant proteins including epithelial cell-transforming sequence 2 oncogene (Ect2) (12), neuronal protein interacting specifically with TC10 (nPIST) (13) and myc-binding protein-2 (MYCBP2)

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Academic Research

An unusual business model involving the most unusual people



Academic Collaborators

One collaborator is many partners with different priorities

Principal Investigator Priorities

- Tenure and Promotion
- Solvency
- Trainees

Other priorities

- Teaching
- Lab/personnel situation
- Risk
- Competition



Institutional Priorities


- Academic freedom
- Protecting faculty and trainees
- Intellectual property

Other priorities


- Business model
- National status
- Politics
- Internal initiatives

Academic Science

There is too much of it, and most of it is wrong

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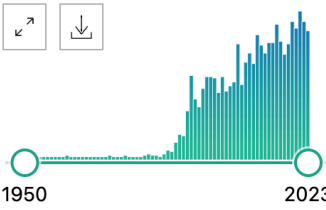
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RESULTS BY YEAR



1950 2023

TEXT AVAILABILITY

☐ Abstract

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1 Maranga C, Fernandes TG, Bekman E, da Rocha ST.

Cite FEBS J. 2020 Jun;287(11):2154-2175. doi: 10.1111/febs.15258. Epub 2020 Mar 14.

PMID: 32087041 [Free article.](#) [Review.](#)

Share **Angelman syndrome** (AS) is an incurable neurodevelopmental disease caused by loss of function of the maternally inherited UBE3A gene. ...

☐ **Angelman Syndrome.**

2 Margolis SS, Sell GL, Zbinden MA, Bird LM.

Cite Neurotherapeutics. 2015 Jul;12(3):641-50. doi: 10.1007/s13311-015-0361-y.

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Share In this review we summarize the clinical and genetic aspects of **Angelman syndrome** (AS), its molecular and cellular underpinnings, and current treatment strategies. ...

A PROPOSED STRUCTURE FOR THE NUCLEIC ACIDS

BY LINUS PAULING AND ROBERT B. COREY

GATES AND CRELLIN LABORATORIES OF CHEMISTRY,* CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated December 31, 1952

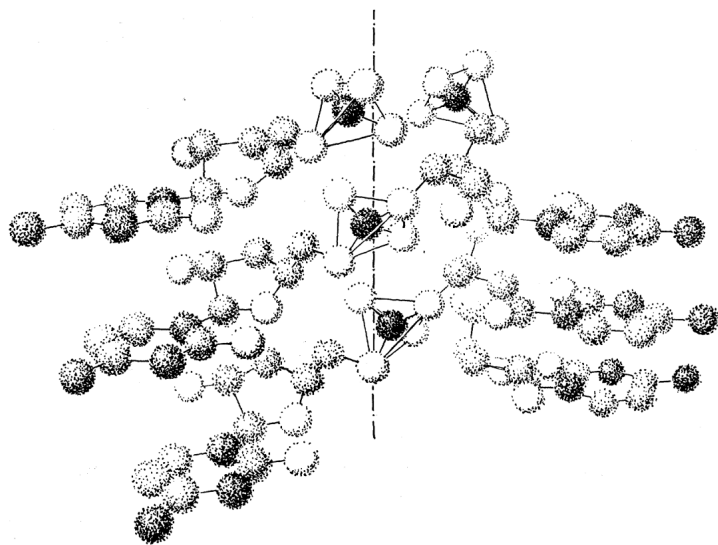


FIGURE 4

Perspective drawing of a portion of the nucleic acid structure, showing the phosphate tetrahedra near the axis of the molecule, the β -D-ribofuranose rings connecting the tetrahedra into chains, and the attached purine and pyrimidine rings (represented as purine rings in this drawing). The molecule is inverted with respect to the coordinates given in table 1.

[Proc Natl Acad Sci U S A. 1953 Feb;39\(2\):84-97. doi: 10.1073/pnas.39.2.84.](#)

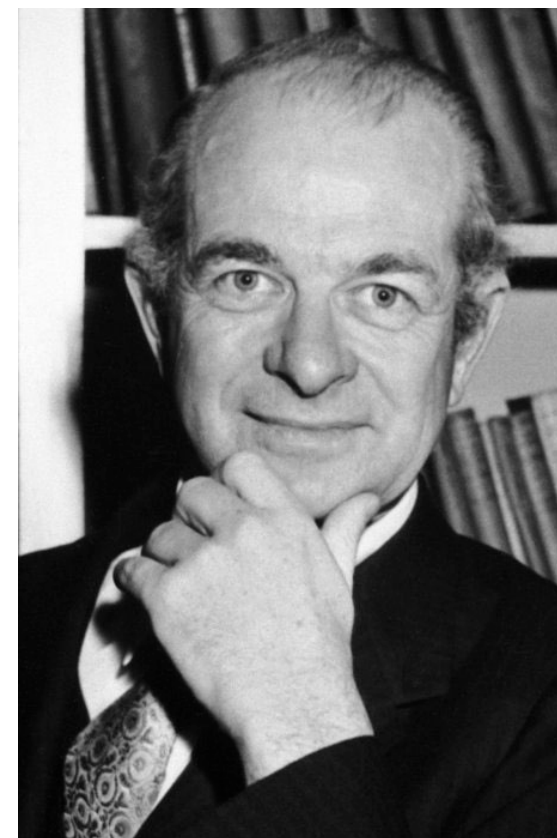
A Proposed Structure For The Nucleic Acids

[L. Pauling](#)¹, [R B Corey](#)

Affiliations + expand

PMID: 16578429 PMCID: [PMC1063734](#) DOI: [10.1073/pnas.39.2.84](#)

[Free PMC article](#)



Linus Carl Pauling

Nobel Peace Prize 1954 and 1962

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid



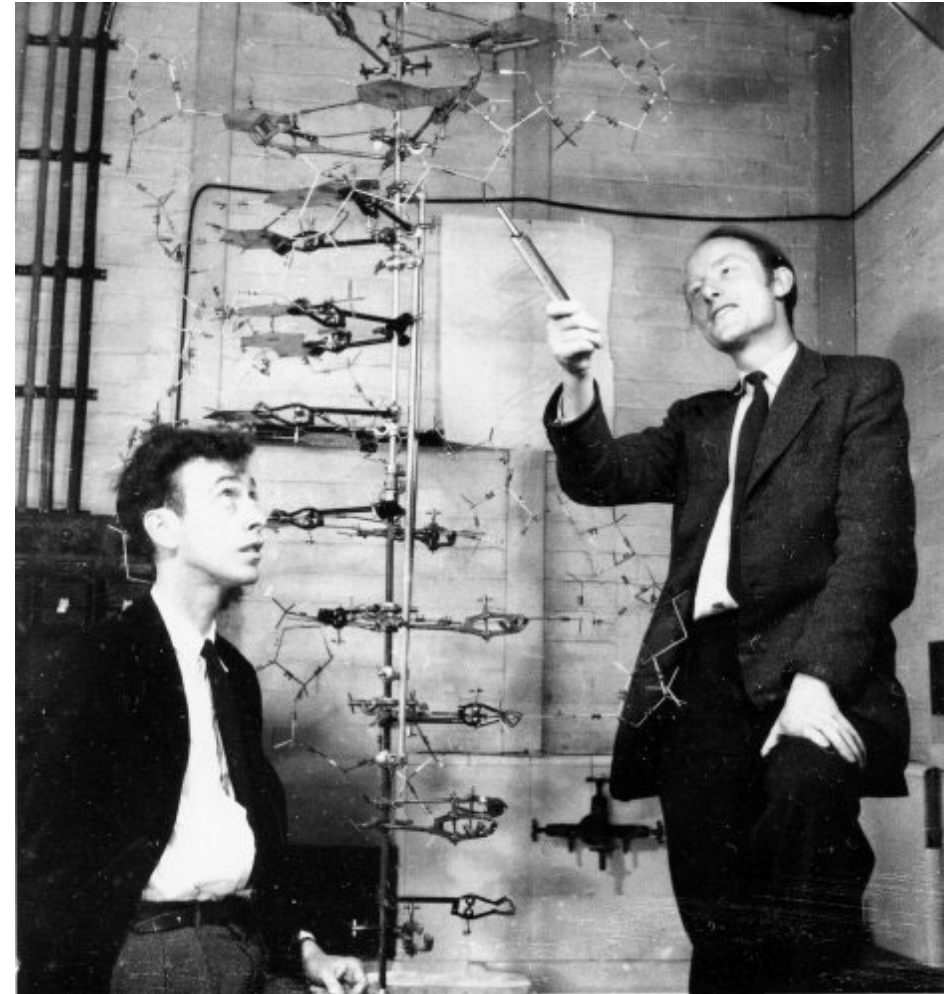
This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

> [Nature](#). 1953 Apr 25;171(4356):737-8. doi: 10.1038/171737a0.

Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid

J D WATSON, F H CRICK

PMID: 13054692 DOI: [10.1038/171737a0](#)

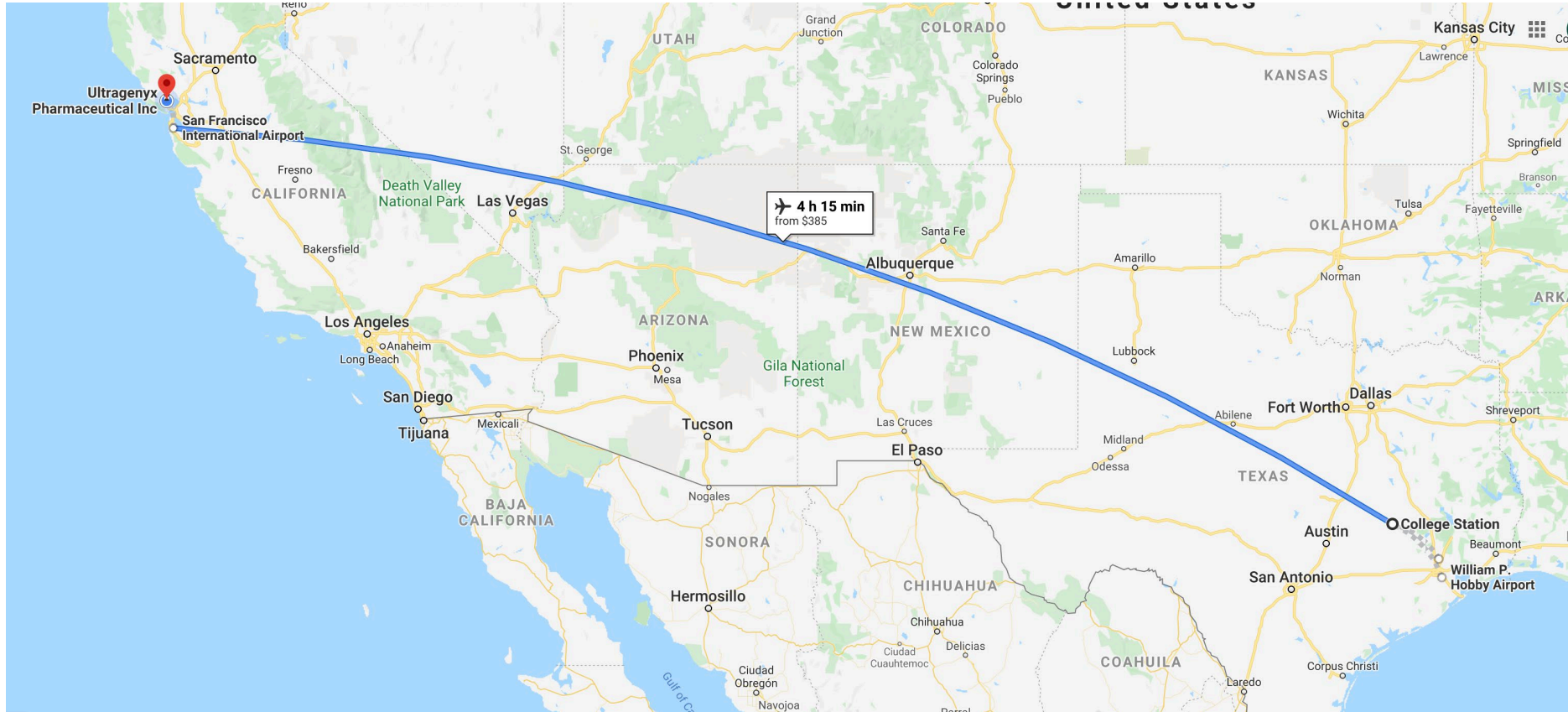


James Watson and Francis Crick

Nobel Peace Prize 1962

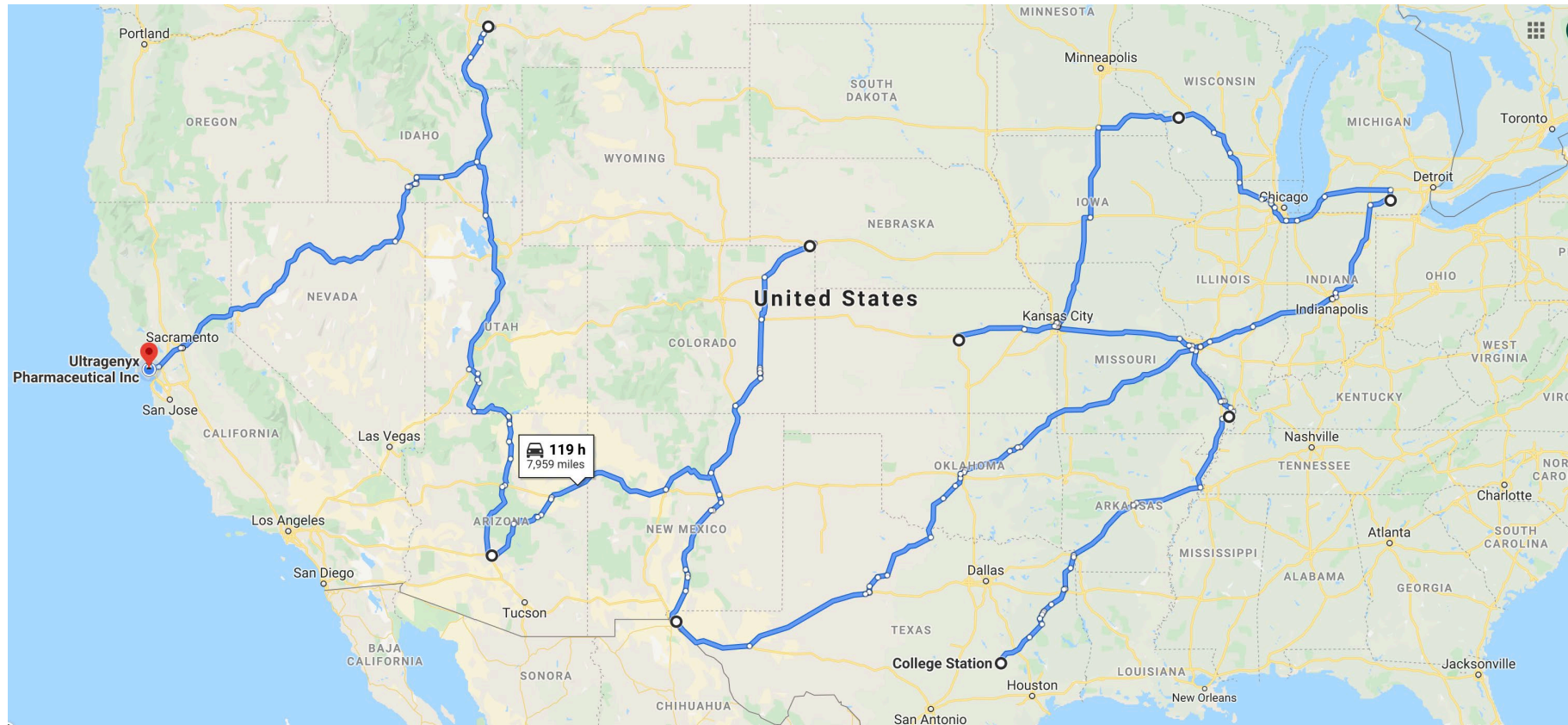
Your Journey with an Academic Collaborator

Expectation



Your Journey with an Academic Collaborator

Reality



Conclusions

- Academic research is the engine that drives innovation, but it is a unique and often misunderstood ecosystem - try to understand it.
- Find a collaborator who understands your objectives and timelines, and try to understand their objectives and timelines – every person and situation is different.
- Trust your academic collaborator, but do not make assumptions about their situation, environment, institution, etc. – find out as much as you can as early as possible.
- Be dubious about scientific publications, scientific claims, timelines, etc. — it is the nature of research to embellish and overpromise.
- Be focused but expect twists and turns and failures and frustrations — they are inevitable.

Thank you!

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